Biogenetic-Type Synthesis of Lupin Alkaloids

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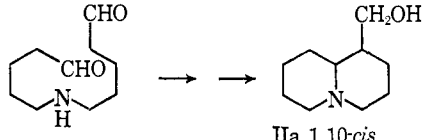
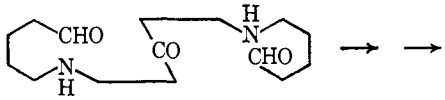
Abstract: The lupinine (II) and the sparteine (IV) systems have been constructed by synthetic schemes based on proposed biosyntheses of these alkaloids.

The lupinine system (II) has been postulated[2] to arise in nature by Mannich-type cyclization of the amine dialdehyde I, formed in the plant by decarboxylative deamination and coupling of two molecules of lysine. Similarly, it has been suggested that the biosynthesis of the alkaloid sparteine (IV) involves initial formation of 8-ketosparteine, formed by cyclization of the diaminoketodialdehyde (III), presumed to arise in nature by decarboxylation, deamination, and coupling of γ-keto-α,α′-diaminopimelic acid and two molecules of lysine.[2a] This paper describes several laboratory syntheses of these two alkaloid systems utilizing the proposed intermediates or closely related compounds.

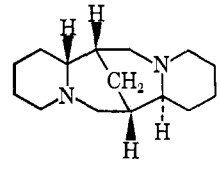


I

IIa, 1,10-*cis*
b, 1,10-*trans*



III

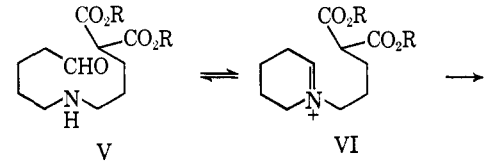


IV

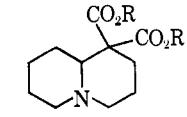
Lupinine (IIa) and Epilupinine (IIb). Although there are many examples of reactions in which the methylene group adjacent to an aldehyde function displays nucleophilic behavior, a more strongly activated methylene or methinyl unit is generally employed in the Mannich reaction. Consequently, certain of our synthesis efforts were directed toward preparation of an intermediate such as V (or its equivalent VI), which was expected to cyclize rapidly to the quinolizidine VII.

Three separate routes featuring the conversion of VI to VII were realized.

In one approach, N-(4,4-dicarboxy-*n*-butyl)pyridinium betaine (VIII) was prepared by alkylation of pyridine with diethyl 3-bromo-*n*-propylmalonate and treatment of the resulting crude quaternary salt with silver oxide. Hydrogenation of the betaine VIII in

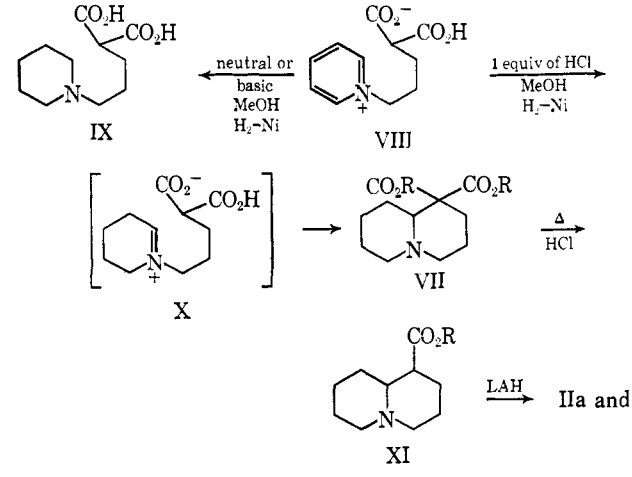


V VI



VII

neutral or basic methanolic solution over nickel or palladium catalysts resulted in the uptake of no less than 3 equiv of hydrogen, the product being, in each case, the undesired monocycle, N-(4,4-dicarboxy-*n*-butyl)piperidine (IX). Subsequent decarboxylation in hydrochloric acid led to the known[3] hydrochloride salt of 5-(N-piperidyl)valeric acid. Selective 2-mole hydrogenation of the betaine (VIII) was achieved, however, when the hydrogenation in methanol over nickel was carried out in the presence of 1 equiv of hydrochloric acid. Decarboxylation of the crude hydrogenation product was accomplished by heating in hydrochloric acid solution, the resulting amino acid being subsequently converted to its ethyl ester (XI, R = Et). Reduction of the ester group by means of lithium aluminum hydride afforded a mixture from which crystalline *dl*-epilupinine and *dl*-lupinine were isolated in a ratio of approximately 4:1. The identities of the two alkaloids were established by elemental analyses, comparison of the infrared spectra with those reported by Marion, *et al.*,[4] and comparison of the melting points of the



IX VIII

X VII

XI

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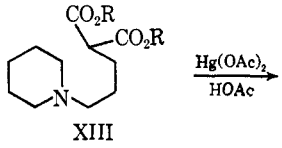
(2) (a) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955, p 74; (b) C. Schöpf, E. Schmidt, and W. Braun, *Ber.*, 683 (1931).

(3) S. M. McElvain and W. B. Thomas, *J. Am. Chem. Soc.*, **56**, 1806 (1934).

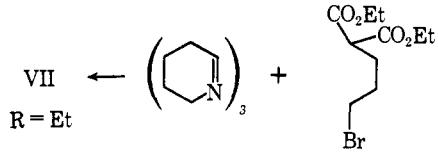
(4) R. Marion, H. J. Vipond, and A. F. Thomas, *Can. J. Chem.*, **33**, 1290 (1955).

parent compounds and their methiodide derivatives with those recorded by Shoppee, *et al.*[5]

The amorphous quinolizidine-1,1-dicarboxylic acid (VII, R = H) was prepared by two additional routes, each of which proceeds by way of VI and VII (R = Et). In one case, N-(5,5-dicarbethoxy-*n*-butyl)piperidine (XIII) was obtained in 89% yield by the reaction of diethyl 3-bromo-*n*-propylmalonate with 2 equiv of piperidine in benzene. Mercuric acetate dehydrogenation of the N-substituted piperidine in 5% acetic acid[6] yielded a crude product showing a weak enamine band at 6.10 μ, which completely disappeared when an aqueous ethanolic solution was allowed to stand several days at room temperature. Distillation provided the 1,1-dicarbethoxyquinolizidine (VII, R = Et) in 55% yield. Alternatively, treatment of Δ^1-piperideine trimer[7] with 3-bromo-*n*-propyl malonate in 70% ethanol afforded directly 1,1-dicarbethoxyquinolizidine in good yield.



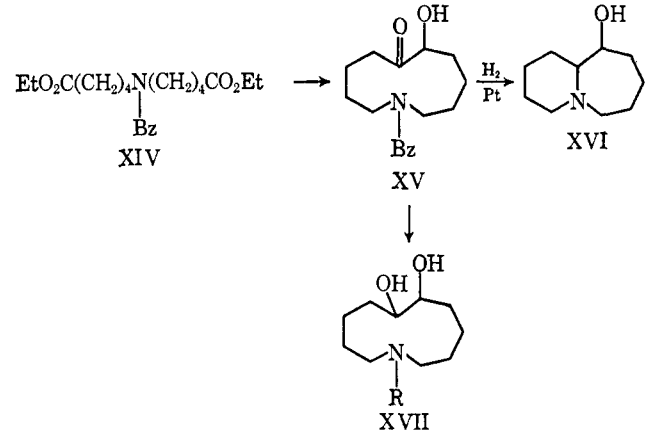
XIII



It was noted that the method of decarboxylation had a decided effect on the ratio of diastereoisomers produced. In contrast to the 4:1 predominance of the thermodynamically favored isomer, epilupinine, characterizing decarboxylation carried out by heating in hydrochloric acid, approximately equal amounts of *dl*-lupinine and *dl*-epilupinine were isolated following esterification and reduction of the product formed by heating the diacid at 165° under nitrogen until the evolution of carbon dioxide ceased. Although various factors which might influence the decarboxylation course can be identified, choice of the crucial effect can hardly be made.

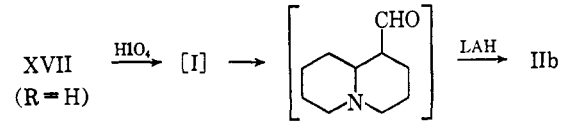
Leaving the Mannich-type cyclization of malonate derivatives, we turned our attention to a more important matter, the preparation and cyclization of the amine dialdehyde, I, presumably a true intermediate in the biosynthesis of lupinine.

The starting material for the synthesis, N-benzyl-N,-N-bis(ω-ethyl *n*-valerate)amine (XIV), was obtained by the alkylation of benzylamine with 2 equiv of ethyl 5-bromovalerate. An acyloin condensation of the amine diester (XIV) gave N-benzylazacycloundecan-6-ol-7-one (XV) in 41% yield. Attempted simultaneous reduction of the carbonyl group and hydrogenolysis of the benzyl group by hydrogenation over platinum in acetic acid gave a crystalline product, mp 67–70°, judged to be the bicyclic amino alcohol, XVI, on the basis of its infrared and ultraviolet spectra as well as its lack of reactivity toward periodic acid. This course of reaction would be expected if debenzylation occurred prior to reduction of the carbonyl group. Consequently, the carbonyl group was first reduced with lithium aluminum hydride followed by hydrogenolysis using palladium on carbon. The resulting azacycloundecane-6,-7-diol (XVII, R = H) was obtained as a waxy, white solid in 82% yield.



XIV XV XVI XVII

A dilute, buffered (pH 5) solution of the amine diol (XVII, R = H) containing periodic acid was allowed to stand at room temperature for 1 day. Under these conditions normal periodate cleavage to the amine dialdehyde I was followed by cyclization. Reduction of the resulting quinolizidine-1-carboxyaldehyde (XVIII) gave a mixture from which *dl*-epilupinine was isolated in 2% over-all yield starting from the amine diol XVII (R = H).



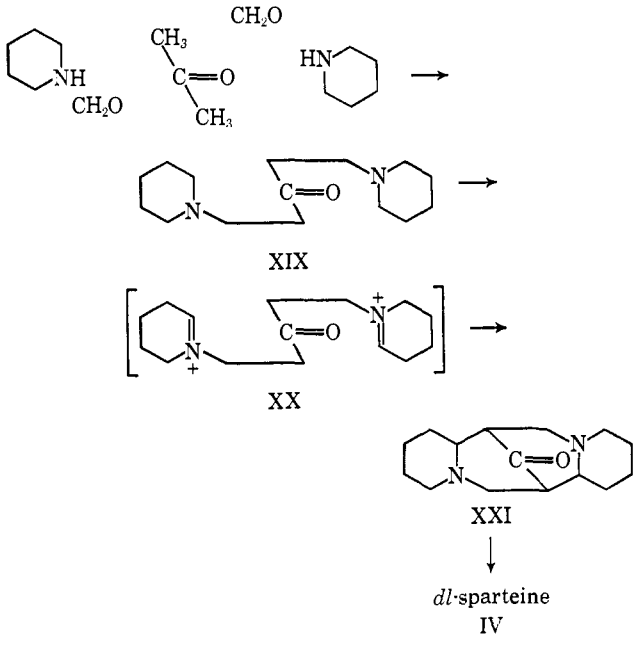
XVIII

The above results suggest that biosynthesis in the lupinine series may involve an essentially spontaneous Mannich-type cyclization, the major enzymic purpose being the formation of precursor amine dialdehyde I.

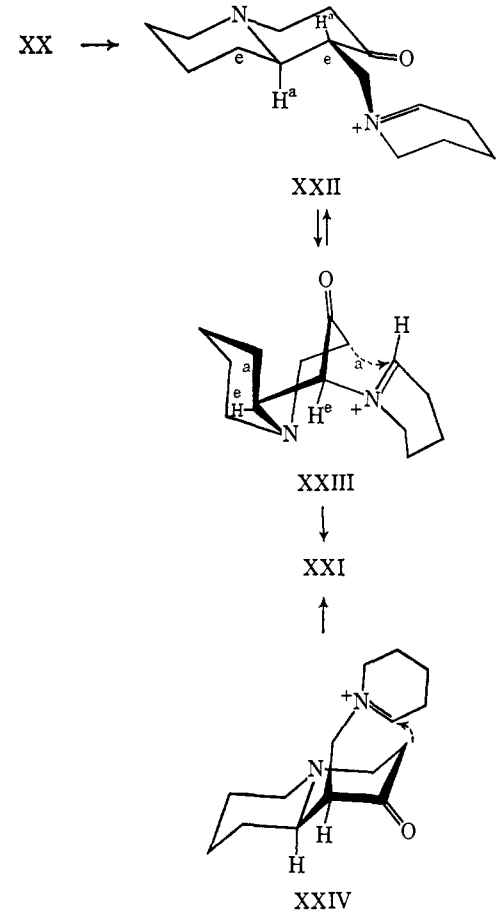
Sparteine (IV). It appeared that by application of the Mannich reaction, the more complex sparteine case might be managed, specifically by preparation of the key precursor, the acyclic keto dialdehyde III. The diiminium ketone XX, a structure equivalent to the proposed biogenetic intermediate III, would be readily accessible by mercuric acetate dehydrogenation of β,β'-di(N-piperidinyl)diethyl ketone (XIX). The dihydrochloride salt of XIX was prepared in 13% yield by a symmetrical bis-Mannich condensation involving 2 equiv each of piperidine hydrochloride and formaldehyde with 1 equiv of acetone in glacial acetic acid. The dihydrochloride salt was converted to the free base and treated with an excess of mercuric acetate in 5% acetic acid. Chromatography of the resulting crude product resulted in the isolation of a colorless crystalline material, mp 71–72.5°, in 10% yield. The infrared spectrum of this material showed no absorption in the enamine region, but exhibited a doublet with peaks at 5.74 and 5.80 μ, attributed to a ketone group. Subsequent identification of the compound as *dl*-8-ketosparteine (XXI) was based on Wolff–Kishner reduction to *dl*-sparteine (IV), which was characterized by comparison

(5) C. W. Shoppee and H. R. Lewis, *J. Chem. Soc.*, 313 (1956).
(6) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, 79, 5279 (1957).
(7) C. Schöpf, H. Arm, and H. Krimm, *Ber.*, 84, 690 (1951).

of the melting points of its salts with those of authentic *dl*-sparteine[8] as well as infrared spectral identity with l-sparteine.



Although the crude product of the mercuric acetate dehydrogenation was not thoroughly examined, 8-ketosparteine appeared to be the sole sparteine-type isomer formed. Stereoselective construction of the sparteine ring system is noteworthy since α-isosparteine is the most stable of the three possible alkaloidal steteoisomers.[9] However, consideration of possible mechanisms by which the transformation of β,β'-di(N-piperidinyl)diethyl ketone (XIX) to 8-ketosparteine (XXI) might occur led to the conclusion that preferential or exclusive formation of the single stereoisomer would not be unreasonable considering the circumstances of this reaction. Assuming that the two new rings, B and C, are closed sequentially, the reaction would be expected to proceed *via* intermediate XXII in which the tetrahydropyridinylmethylene substituent is in the equatorial conformation. Even if this substituent in the initially formed quinolizidine system were generated in the axial conformation (*i.e.*, *cis* relationship), epimerization to the more stable equatorial conformation should occur readily under the conditions of the reaction since enolization of the original ketone function must have occurred in order for the initial ring closure to have taken place. For intermediate XXII to undergo the second ring closure it would have to perform as the less stable conformer, XXIII; cyclization would then result in the formation of *dl*-8-ketosparteine (XXI), the *more* stable possibility at this point. Alternatively, one can imagine a sequence starting from the less stable *cis* isomer of XXII, which would have to appear as the conformer XXIV for cyclization to ketosparteine with generation of the *less* stable stereochemical arrangement in this final step. In any case, the above laboratory operations constitute a simple, three-step laboratory synthesis of sparteine, starting from inexpensive, stockroom starting materials.



Experimental Section

All melting points which are designated as *corrected* were taken in open capillary tubes in a Hershberg apparatus using Anschütz total immersion calibrated thermometers. All melting points which are designated as *uncorrected* were taken on a hot stage and are approximately corrected for stem exposure. Boiling points are uncorrected.

Analyses were performed by the Microanalytical Laboratory of the University of Wisconsin, by the Huffman Microanalytical Laboratories, Wheatridge, Colo., or by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Infrared spectra were taken in chloroform solution, on a Baird double-beam self-recording spectrophotometer unless otherwise specified. Ultraviolet spectra were taken in 95% ethanol solution on a Cary recording spectrophotometer (Model 11 MS) unless otherwise specified.

All solvents used for chromatography, reaction mixtures, or recrystallizations were reagent grade solvents, used without further purification unless otherwise specified, with the exception of benzene, acetone, nitromethane, and petroleum ether. These four solvents were distilled prior to use.

N-(4,4-Dicarbethoxy-*n*-butyl)piperidine (XIII, R = Et). A mixture of 10 g (0.0334 mole) of diethyl 3-bromopropylmalonate,[10] bp 154–157° (9 mm), 6.60 ml (0.668 mole) of piperidine, and 30 ml of benzene was allowed to stand at room temperature for 3 days. The white, crystalline piperidine hydrobromide (mp 231–233°) was collected on a filter and washed with ether. The combined benzene and ether filtrates were washed with water and dried over anhydrous magnesium sulfate. After removing the drying agent by filtration, the ether was removed by distillation. Fractional distillation of the product afforded 8.48 g (89%) of a colorless liquid, bp 134–135° (0.2 mm).

Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54. Found: C, 63.05; H, 9.42.

The methiodide derivative, after one recrystallization from ether, melts at 103–104° uncor.

N-(4,4-Dicarboxy-*n*-butyl)pyridinium Betaine (VIII). A solution of 10.0 ml (0.123 mole) of pyridine and 19.5 g (0.0651 mole) of

(8) N. J. Leonard and R. E. Beyler, *J. Am. Chem. Soc.*, 72, 1316 (1950).

(9) N. J. Leonard, "The Alkaloids," R. H. F. Manske, Ed., Vol. VII, Academic Press, New York, N. Y., 1960, Chapter 14.

(10) R. Willstatter and F. Ettlinger, *Ann.*, **326**, 99 (1902).

diethyl 3-bromopropylmalonate, bp 154–157° (9 mm), in 30 ml of anhydrous ethanol was maintained at 75° for 24 hr. The resulting reddish solution was concentrated by distillation under reduced pressure and taken up in 200 ml of water. The aqueous solution was washed with three 50-ml portions of ether to remove unreacted starting material. Freshly prepared silver oxide was added to the aqueous solution in small portions with trituration until addition of the brownish silver oxide no longer formed yellow silver bromide. The precipitate was removed by filtration and the clear filtrate was found to be slightly basic and free of bromide ions as shown by the silver nitrate test for halides. After heating the aqueous solution at 75° under a nitrogen atmosphere for 4 hr, the excess water was removed by distillation under reduced pressure. Removal of the final traces of water and pyridine by lyophilization afforded 15.2 g of a yellowish powder. After crystallization from freshly distilled nitromethane, 12.7 g (88%) of cream colored crystals were obtained, λ_{max} 258 mμ (ε 4410). Four crystallizations from methanol and ether afforded colorless crystals which underwent decomposition with evolution of carbon dioxide when heated to 126°.

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87. Found: C, 58.82; H, 6.18.

1,1-Dicarbethoxyquinolizidine (VII, R = Et). A. Mercuric Acetate Dehydrogenation of N-(4,4-Dicarbethoxy-*n*-butyl)piperidine (XIII, R = Et). To a solution of 325 g (1.02 moles) of mercuric acetate in 860 ml of 5% acetic acid was added 61.0 g (0.214 mole) of N-(4,4-dicarbethoxy-*n*-butyl)piperidine (XIII, R = Et), bp 134–135° (0.2 mm). The solution was heated at 95° with stirring for 0.75 hr. Mercurous acetate began to precipitate within 5 min. After cooling the mixture in an ice bath, the mercurous acetate was removed by filtration and washed with 5% acetic acid solution. The mercurous acetate was then washed with acetone and dried in a vacuum desiccator, and was found to weigh 93 g (0.359 mole), 84% of the calculated amount. Hydrogen sulfide gas was allowed to bubble through the combined filtrate and aqueous washings until no further precipitation took place. The mercuric sulfide was removed by filtering the mixture through a preformed Filter-Cel pad. The clear, slightly yellow filtrate was adjusted to a pH of 6.5 by addition of solid potassium carbonate and allowed to stand at room temperature overnight. After the solution was cooled in an ice bath and saturated with potassium carbonate, it was extracted five times with 500-ml portions of ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The yellow oil obtained after removal of the magnesium sulfate by filtration and the ether by distillation under reduced pressure was fractionally distilled, affording 33.5 g (55%) of colorless oil, bp 140–147° (5 mm), $n^{29}D$ 1.4720.

Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.51; H, 8.95; N, 5.20.

The methiodide derivative, after three crystallizations from ethanol–water, melts at 145.5–146.5 uncor.

B. Alkylation of Δ¹-Piperideine with Diethyl 3-Bromopropylmalonate. To 110 ml of a 70:30 ethanol–water mixture was added 39 g (0.13 mole) of diethyl 3-bromopropylmalonate, bp 154–157° (9 mm), and 10 g (0.12 mole) of α-tripiperideine,[11] mp 60.5–62.0°. The mixture was swirled until it was homogeneous and was then allowed to stand in the dark at room temperature. After 4 days the solution was concentrated by distillation under reduced pressure, made acidic by the addition of 50% hydrochloric acid, and extracted several times with ether. From the combined ether extracts, 22.6 g of diethyl 3-bromopropylmalonate was obtained. The acidic aqueous solution was made basic by the addition of potassium carbonate and extracted five times with 50-ml portions of ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried over magnesium sulfate. After removal of the drying agent by filtration and the ether by distillation, the resulting colorless oil was distilled, affording 11.7 g of an oil, bp 142–144° (3–5 mm), having an infrared spectrum identical with that of the 1,1-dicarbethoxyquinolizidine (VII, R = Et) obtained in procedure A.

The amount of product obtained corresponded to a 34% yield based on the amount of starting material used, or to an 81% yield based on the amount of diethyl 3-bromopropylmalonate consumed.

1,1-Dicarboxyquinolizidine (VII, R = H). A. Catalytic Hydrogenation of N-(4,4-Dicarboxy-*n*-butyl)pyridinium Betaine (VIII). The catalyst, 200 mg of Raney nickel W-2, was added to 10 ml of absolute methanol in a hydrogenation flask and stirred under a hydrogen atmosphere at room temperature until no further change in the volume of hydrogen occurred. A methanolic solution containing 1.51 g (6.75 mmoles) of N-(4,4-dicarboxy-*n*-butyl)pyridinium betaine (dec pt 126°) and 6.75 ml (6.75 mmoles) of 1 *N* hydrochloric acid was added to the hydrogenation flask. The mixture was stirred until no further hydrogen was taken up. Since a small amount of hydrogen gas was continually produced by the reaction of the mildly acidic solution with the nickel catalyst, a quantitative determination of the hydrogen uptake could not be made. The catalyst was removed by means of centrifugation and the greenish supernatant was made just basic by the addition of several drops of ammonium hydroxide. A solution of ammonium sulfide was added until no further precipitation of nickel sulfide occurred. The precipitate was completely removed by centrifugation followed by filtration through Filter-Cel. The clear filtrate was neutralized by the addition of hydrochloric acid and concentrated by distillation under reduced pressure and below 50°. The various purification procedures that were attempted failed to yield a crystalline product. Therefore the crude material was carried on to the next step, decarboxylation to 1-carboxyquinolizidine (XI, R = H), without further characterization or purification.

B. Saponification of 1,1-Dicarbethoxyquinolizidine (VII, R = Et). A mixture of 35.2 g (0.125 mole) of 1,1-dicarbethoxyquinolizidine and 20.0 g (0.30 mole) of potassium hydroxide (85%) in 150 ml of 95% ethanol was stirred at room temperature for 2 days. The alcoholic solution was neutralized by titration with hydrochloric acid. Removal of the solvent by distillation under reduced pressure and below 50° left a viscous syrup. The mixture of inorganic salt and crude product was used directly in the next step, decarboxylation to 1-carbethoxyquinolizidine.

1-Carboxyquinolizidine (XI, R = H). A. Acidic Decarboxylation of 1,1-Dicarboxyqinolizidine (VII, R = H). A crude mixture of 1,1-dicarboxyquinolizidine and inorganic salt was dissolved in constant-boiling hydrochloric acid and the resulting solution heated under reflux until no further carbon dioxide was evolved. The water was removed by distillation under reduced pressure. Additional water was added and also removed by distillation. To the resulting gummy residue was added absolute ethanol and the mixture triturated while being heated on a steam bath. When the solid material had become white and powdery the mixture was cooled in an ice bath and the inorganic salt removed by filtration. After removal of the ethanol by distillation the resulting yellowish, gummy material was dissolved in water and treated with an excess of freshly prepared silver carbonate.[12] The mixture was stirred in the dark for 10 min, the solid removed by filtration and the filtrate tested for halide ion by means of the silver nitrate test. Removal of the water by distillation yielded a yellow solid. Acetone containing about 10% absolute ethanol was added and the mixture heated over a steam bath and triturated until the solid became nearly white. The powdery material was collected on a filter and dried in a vacuum desiccator. The over-all yield of crystalline product based on the weight of 1,1-dicarbethoxyquinolizidine was 70% of theoretical.

The amino acid was recrystallized by adding a tenfold quantity of acetone, heating on a steam bath, and adding water slowly until all of the solid was dissolved. When the solution was cooled, colorless, needlelike crystals were formed, mp 255–260° with decomposition. The point of decomposition was dependent on the rate of heating. An analytical sample was prepared by allowing the amino acid to sublime at 150° (5 mm).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.71; H, 9.24; N, 7.65.

B. Thermal Decarboxylation of 1,1-Dicarboxyquinolizidine (VII, R = H). A crude mixture of 1,1-dicarboxyquinolizidine and inorganic salt was heated on an oil bath at 165° under a nitrogen atmosphere. After the effervescence ceased the brownish, crusty material was cooled, absolute ethanol added, and the mixture triturated over a steam bath. When the solid material had become white and powdery the mixture was cooled and the inorganic salt collected on a filter. Removal of the ethanol by distillation yielded a gummy material which was dissolved in water, treated with silver carbonate, and worked up as described in procedure A.

1-Carbethoxyquinolizidine (XI, R = Et). After drying the crude mixture of 1-carboxyquinolizidine (XI, R = H) and inorganic salt obtained from the decarboxylation of 1,1-dicarboxyquinolizidine

(11) C. Schöopf, A. Komzak, F. Braun, and E. Jacobi, *Ann.*, **559**, 21 (1948).

(12) "Inorganic Syntheses," T. Moeller, Ed., Vol. V, McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 19.

(VII, R = H), it was dissolved in anhydrous ethanol. Dry hydrogen chloride gas was bubbled through the alcohol solution for 10–15 min. The solution was heated under reflux for 3 hr and the ethanol removed by distillation. The resulting yellow oil was cooled in an ice bath, covered with ether, and enough cold 30% potassium hydroxide solution added to make the mixture basic. After extracting the aqueous layer four times with ether, the combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration and the ether by distillation, and fractional distillation of the crude oil, afforded a clear, colorless liquid, bp 154–156° (20 mm) [lit.[13] bp 95–100° (1.0 mm)].

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 67.98; H, 10.04.

Without purifying the intermediates, 1-carbethoxyquinolizidine (XI, R = Et) was obtained in 53% yield based on the amount of N-(4,4-dicarboxy-*n*-butyl)pyridinium betaine (VIII) used, or in better than 47% yield based on the amount of 1,1-dicarbethoxyquinolizidine (VII, R = Et) used.

***dl*-Lupinine (IIa) and *dl*-Epilupinine (IIb).** The procedure reported by Boekelheide, *et al.*,[13] was utilized for the reduction of 1-carbethoxyquinolizidine (XI, R = Et) to 1-hydroxymethylquinolizidine with lithium aluminum hydride except that the product was not distilled, but dissolved in petroleum ether (bp 60–68°) and chromatographed.

Adsorption alumina, Fischer Lab. Chem. A-540, was used as the adsorbent and the column developed by gradient elution, proceeding from petroleum ether to benzene to diethyl ether to chloroform. *dl*-Lupinine was collected in fractions containing 100% benzene to ether–benzene (1:4) and was crystallized from petroleum ether (bp 60–68°), mp 58.3–59.8° uncor (lit.[14] mp 59°).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.32; K, 8.28. Found: C, 70.95; H, 11.33; N, 8.12.

The methiodide derivative melts with decomposition at about 285° (lit.[5] mp 288–289°) after crystallization from absolute ethanol.

dl-Epilupinine was obtained from fractions consisting of ether–benzene (1:3) to 100% ether and was crystallized from petroleum ether (bp 60–68°), mp 81.2–82.0°. No depression of the melting point occurred when the sample was mixed with *dl*-epilupinine obtained from Professor Boekelheide.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.32; N, 8.28. Found: C, 70.95; H, 11.23; N, 8.38.

The infrared spectra of both compounds were identical with those reported by Marion, *et al.*[4]

Ethyl 5-Bromovalerate. In a flask fitted with an efficient reflux condenser were mixed 30 ml of 95% ethanol, 13 ml of concentrated sulfuric acid, and 20 g (0.123 mole) of commercial 4-bromovaleronitrile. The mixture was heated at reflux with stirring for 7 hr. After cooling in an ice bath, 100 ml of cold water was added and the solution immediately extracted with four 100-ml portions of diethyl ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the ether by distillation left a colorless liquid, which was then distilled. Two fractions were kept, 4.1 g being collected between 105 and 116° (20 mm), $n^{25}D$ 1.4555 [lit.[15] bp 107° (15 mm), $n^{20}D$ 1.4585]. The total weight of the distilled product corresponded to a 90% yield. The infrared spectrum (liquid film) showed a strong absorption band at 5.80 μ and the absence of a band in the 4.0–5.0-μ region.

Diethyl N-Benzyl-N,N-bis(ω-*n*-valerate)amine (XIV). A solution of 62.7 g (0.3 mole) of ethyl 5-bromovalerate, bp 116–119° (20 mm), 16.4 ml (0.15 mole) of distilled benzylamine, and 300 ml of ethyl alcohol was mechanically stirred at room temperature overnight. The clear, colorless solution was then refluxed with stirring for 4 hr, 25 g of potassium carbonate added, and refluxing continued for another 8 hr. The solvent was removed by distillation under gradually decreased temperature and pressure. An excess of 1 *N* hydrochloric acid was added to the viscous concentrate and the mixture extracted four times with 100-ml portions of diethyl ether. The aqueous solution was cooled in an ice bath and made basic by the addition of solid potassium carbonate. Ether was then added and the aqueous layer concentrated with potassium carbonate. The saturated solution was extracted four more times with ether and the combined ether extracts dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration and the ether by distillation left approximately 35 ml of a viscous oil which was distilled twice, affording 15.3 g (28%) of a colorless oil, bp 193–194° (0.8 mm).

Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.76; H, 9.02; N, 4.75.

N-Benzylazacycloundecan-6-ol-7-one (XV). The procedure used is similar to that reported by Leonard, *et al.* Approximately 1.5 l. of xylene was distilled from sodium and collected in a 2-l. three-necked flask. One-half of the distillate was in turn redistilled from the three-necked flask in order to remove all traces of moisture from the apparatus. To the xylene remaining in the flask was added 4.0 g (0.17 g-atom) of freshly cut sodium, and the system swept with purified nitrogen. After melting the sodium by heating the xylene to reflux, the metal was finely dispersed by means of a Model E-1 Vibromixer, set at maximum noise level. While continuing the heating, vibration, and nitrogen sweep, 15.3 g (0.0421 mole) of diethyl N-benzyl-N,N-bis(ω-*n*-valerate) (XIV), bp 193–194° (0.8 mm), dissolved in 100 ml of dried and distilled xylene, was added by means of a Hershberg dropping funnel attached to the top of a reflux condenser at a rate which required 4.5 hr for completion. The nitrogen sweep was continued while the mixture was kept at reflux and vibrated for another 0.5 hr. The mixture was cooled slowly while increasing the input of nitrogen. Finally the flask was cooled in an ice bath and 10 ml of glacial acetic acid added cautiously to the moderately vibrated solution. The pH of the mixture was found to be just on the acidic side of 7. The precipitated sodium acetate was dissolved by the addition of 300 ml of water, which was then saturated with potassium carbonate. The two layers were separated and the aqueous layer extracted three times with 100-ml portions of ether. The combined organic extracts were dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration and the solvents by distillation at reduced pressure, the resulting crude yellow oil was vacuum distilled, affording 4.76 g (41%) of a colorless, viscous oil, bp 170–172° (0.2 mm).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.03; H, 9.02.

N-Benzylazacycloundecane-6,7-diol (XVII, R = Bz). To 15 ml of a 1.2 *M* ether solution of lithium aluminum hydride was added 1.96 g (7.12 mmoles) of N-benzylazacycloundecan-6-ol-7-one (XV), bp 170–172° (0.2 mm). When the addition was complete, the solution was heated under reflux for 2 hr. The excess hydride was destroyed by the controlled addition of moist ether. Dilute sulfuric acid was added to dissolve the colloidal precipitate and the ether layer extracted three more times with dilute acid. The combined acid extracts were made basic by the addition of potassium hydroxide and extracted with ether by means of a continuous extractor operating for 12 hr. The ether extract was dried over anhydrous sodium sulfate. Removal of the drying agent by filtration and the ether by distillation left 1.7 g of a yellow, viscous oil which was not purified. The infrared spectrum of the crude oil showed no absorption band in the 5.8–6.0-μ carbonyl region.

Azacycloundecane-6,7-diol (XVII, R = H). The catalyst, 600 mg of 10% palladium on carbon, was added to 20 ml of absolute ethanol in a hydrogenation flask and stirred at room temperature under a hydrogen atmosphere until no further change in the volume of hydrogen occurred. An ethanolic solution of 1.28 g (4.61 mmoles) of the crude N-benzylazacycloundecane-6,7-diol was added through the side arm of the hydrogenation flask and stirring begun. A total of 125 ml of hydrogen (108% of calcd) was consumed over a 5-hr period. Removal of the catalyst by filtration and the ethanol by distillation afforded 0.81 g (94%) of a white solid which could not be readily crystallized. An ultraviolet analysis of the ethanol distillate indicated the presence of approximately the calculated amount of toluene.

***dl*-Epilupinine (IIb) *via* Periodate Oxidation of Azacycloundecane-6,7-diol (XVII, R = H).** To 100 ml of a freshly prepared 0.05 *M* sodium acetate–acetic acid (1:1) buffered solution containing 0.400 g (2.13 mmoles) of azacycloundecane-6,7-diol was added 100 ml of buffered solution containing 0.486 g (2.13 mmoles) of periodic acid. The resulting solution was kept in the dark at room temperature for 24 hr. At the end of this period an ultraviolet analysis[16] indicated that a minimum of 70% of the periodate had been converted to iodate. Iodometric analysis of the course of the reaction was found to be unsatisfactory. The cloudy reaction mixture was

(13) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.*, 75, 3243 (1953).

(14) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937).

(15) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, 76, 5708 (1954).

(16) G. V. Marinetti and G. Rouser, *ibid.*, 77, 5345 (1955).

extracted with diethyl ether by means of a continuous extractor operating overnight. After separating the two layers, the now clear aqueous layer was made basic by the addition of potassium carbonate and again extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate. After removal of the drying agent the solution was concentrated by distillation under reduced pressure and below 40°.

No attempt was made to isolate the desired amino aldehyde, but rather the concentrated (60 ml) ether solution of the product was added dropwise to 25 ml of a 1.27 *M* solution of lithium aluminum hydride in ether. When the addition was complete the reaction mixture was heated at reflux for 4 hr. Approximately 50 ml of moist ether was added slowly to destroy the excess hydride. The precipitated metal hydroxides were collected in a sintered-glass funnel and triturated three times with hot chloroform. The ether filtrate and chloroform solutions were combined and dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration and the solvent by distillation afforded 0.215 g of a brown oil. All but 14 mg of this material dissolved in 10 ml of benzene and was chromatographed on 20 g of adsorption alumina. Gradient elution was employed, proceeding from benzene to diethyl ether to chloroform. No significant amount of nonvolatile material was collected until elution with 10% chloroform in ether began. The infrared spectra of the material in the fractions eluted with 10–60% chloroform in ether indicated the presence of *dl*-epilupinine. These fractions were combined, dissolved in hot petroleum ether (60–68°), seeded with a crystal of authentic *dl*-epilupinine.

The infrared spectrum of the crystalline product was identical with that of authentic *dl*-epilupinine.[4]

β,β′-Di(N-piperidinyl)diethyl Ketone Dihydrochloride (XIX). To a mixture of 122 g (1 mole) of piperidine hydrochloride, 30 g (1 mole) of paraformaldehyde, and 200 ml of glacial acetic acid was added 37 ml (0.5 mole) of acetone. The flask, equipped with a reflux condenser, was heated on a steam bath with occasional swirling until the solution became clear. After 3 hr of refluxing the acetic acid was removed by distillation under reduced pressure. The resulting slurry was triturated with 250 ml of hot acetone and filtered. The acetone-insoluble, crystalline material was found to be a mixture of several amine hydrochloride salts from which the desired product could be obtained in a pure state by making use of its relative insolubility in hot chloroform. The crude mixture was triturated in hot chloroform and the insoluble crystals were collected by filtration. The filtrate was evaporated to dryness, and the resulting residue was again extracted with hot chloroform. By repeating this procedure several times a total yield of 21.7 g (13%) of β,β′-di(N-piperidyl) diethyl ketone dihydrochloride was obtained, mp 212–214° (lit.[3] mp 212–214°). Repeated crystallization from methanol–ether raised the mp to 217–219°.

The semicarbazone of the free diamino ketone melts at 94–96° (lit.[3] mp 96–97°). The recrystallized product gave a negative iodoform test.

***dl*-8-Ketosparteine (XXI).** A mixture of β,β′-di-(N-piperidyl) diethyl ketone, prepared from 6.75 g (0.021 mole) of the dihydrochloride salt, and 60 g (0.19 mole) of mercuric acetate in 220 ml of 5% acetic acid (95% water) was heated at 95° with stirring for 1 hr. Precipitation began to occur after approximately 5 min of heating. The reaction mixture was cooled in an ice bath, filtered, and the precipitate washed with 5% acetic acid. After drying, the mercurous acetate weighed 15.9 g (73% of the calculated amount). The filtrate was cooled in an ice bath and hydrogen sulfide bubbled through it for 15 min. After the mixture was filtered through Filter-Cel a clear, slightly yellow solution was obtained which gave to further precipitation when treated with more hydrogen sulfide. Basification of the cooled filtrate was carried out by adding small portions of potassium carbonate until no more gas was evolved. The aqueous solution was covered with a layer of ether, saturated with potassium carbonate, and extracted with four more portions of ether. The combined ether extracts were washed once with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the magnesium sulfate by filtration and the ether by distillation under reduced pressure gave a yellowish oil which was chromatographed on 80 g of adsorption alumina. The column was wet-packed with petroleum ether (bp 60–68°) and developed by gradient elution, proceeding from petroleum (bp 60–68°) ether to benzene to ethyl ether to chloroform. The first nonvolatile material was eluted from the column when the eluent consisted of a 1:1 ratio of benzene and ether, and was found to be *dl*-8-ketosparteine which, after several crystallizations from petroleum ether, melted at 71.0–72.5°.

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.53; H, 9.74; N, 11.28. Found: C, 72.55; H, 9.79; N, 11.08.

The yield of 8-ketosparteine based on the combined weights of the fractions comprising the first chromatographic band was 10% (0.53 g).

***dl*-Sparteine (IV).** The Huang-Minlon modification of the Wolf–Kishner reduction was employed. Four pellets of 85% potassium hydroxide were dissolved in 10 ml of diethylene glycol by stirring at 100° in a flask equipped with a take-off condenser and a nitrogen inlet. The solution was cooled, and 177 mg (0.713 mmole) of *dl*-8-ketosparteine (XXI), mp 71–72.5°, was added followed by 5 ml of additional diethylene glycol. When the solution had been heated for 0.5 hr at 75°, 2 ml of 99–100% hydrazine hydrate was added and the solution stirred at 75° under nitrogen sweep for 1 hr. The temperature was increased to 120° over a period of 1 hr and maintained at that temperature for 0.5 hr. The stopcock connecting the take-off condenser and the reaction flask was closed and the temperature slowly increased to 200° and maintained at that temperature for 1.5 hr. After cooling, the diethylene glycol solution was taken up in water and the water solution washed four times with ether. The combined ether extracts were washed twice with water, once with a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. Removal of the sodium sulfate by filtration and the ether by distillation left 29.4 mg of a colorless oil which exhibited an infrared spectrum nearly identical with that of authentic *l*-sparteine, bp 173° (8 mm), prepared from commercial sparteine sulfate.

In order to account for the remainder of the product the liquid collected beneath the take-off condenser was taken up in water, extracted with ether, dried, and found to contain 76.0 mg of a colorless oil, identical with that obtained from the reaction mixture. The combined crude product was sublimed at 75° (0.5 mm), affording 95 mg (57%) of a colorless oil.

The monoperchlorate salt was prepared as described by Leonard[8] and recrystallized twice from ethanol–ether, mp 131–133° uncor (lit.[8] mp 130–132°). A portion of the monoperchlorate salt was reconverted into the free base, and the infrared spectrum of this material was found to be superimposable on the infrared spectrum of authentic *l*-sparteine.

The dipicrate salt was prepared by adding an excess of picric acid dissolved in ethanol to an ethanolic solution of the free base. An immediate precipitation of yellow crystals occurred. After heating the slurry on a steam bath for 15 min, it was cooled and the crystals were collected on a filter. Four recrystallizations from ethanol afforded rod-shaped crystals, mp 206–208° uncor (lit.[8] mp 207–208°).

The monopicrate salt was obtained by adding 10 mg of the product dissolved in ethanol to an ethanolic solution of an equal weight of picric acid. More ethanol was added and the mixture heated on a steam bath until all of the precipitate had dissolved. The yellow, amorphous precipitate which formed when the solution was cooled was removed by filtration and again dissolved in hot ethanol. Cooling resulted in the formation of organge prisms, mp 132–134° uncor (lit.[8] mp 136–137° after four crystallizations from ethanol).

Preparation of the bisulfate derivate was accomplished by reconverting 19 mg of the perchlorate salt of the product (mp 13–133°) into the free base, which was taken up in 2 ml of ether and treated with 1 drop of concentrated sulfuric acid. The resulting mixture was warmed briefly and then cooled. Vigorous stirring and scratching with a glass rod converted the colorless, ether-insoluble oil into a gummy mass. The ether was removed by decantation and a small quantity of methanol added. By warming the mixture a clear solution was obtained. Addition of ether caused a white, crystalline precipitate to form which was removed by filtration. Recrystallization from methanol–ether afforded a white, crystalline solid, mp 248–250° with decomposition (lit.[8] mp 254° with decomposition).

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